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REVIEW ARTICLE

A SYSTEMATIC REVIEW OF PANDEMIC COVID-19 BASED ON LIVER ENZYMES

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ABSTRACT: Background and Aim: This article aims to analyze liver enzymes in relation to COVID-19 patients by performing a systematic review of articles which describe the changes in liver enzymes in COVID 19. Abnormalities of liver enzymes associated with Covid-19 has been well documented by a number of articles since the start of the pandemic and could be used to monitor the disease progression. hence, this review was done to understand better the effect of covid 19 on liver enzymes. **Methods:** A systematic review to describe existing literature with regard to liver enzyme changes in SARS CoV-2 disease to understand the pattern of variations in ALT and AST. Articles for Literature review were accessed from the PubMed and other sources.On the day of admission and during hospitalization, LFT was done in COVID-19 patients. Median age 47 years (Inter Quarantile Range 33-61). The age group and cut off values for LFT is based on the Institutional board of the "National Health Commission of China". **Result:** We reviewed original articles from 15 International Journals related to COVID-19 and liver enzymes and found that the liver enzymes (ALT, AST) are significantly elevated in pre-existing and non-pre-existing liver disorder in COVID-19 patients. In the present study we have analysed 2811 patients (which were described in the reviewed original articles) with both pre- and non-pre-existing liver injury. Out of 2811 patients the AST was elevated in 471 patients and ALT was elevated in 530 patients.Among them 2,279 patients are with pre-existing liver disease, where AST elevated in 371(25.53%) and ALT was elevated in 401(23.87%) patients. 532 patients are with non-pre-existing liver disease, where AST elevated in 100 (26.6%) and ALT in 129 (21.7%) patients. **Conclusion:** Liver enzymes are elevated both in the pre-existing and non-existing liver disease in COVID-19 patients. Although increase in ALT and AST was more noticed in patients with pre-existing liver disease, a significant percentage of patients without any pre-existing liver abnormalities also showed a high transaminase value.

KEYWORDS: Alanine transaminase (ALT) Aspartate amino transaminase (AST).

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INTRODUCTION:

Severe acute respiratory syndrome coronavirus-2 (COVID -19) has become global threat to human health, which has expanded globally from Wuhan, China in JAN- 2020. SARS- Cov 2 is named as "COVID-19" and later the infection is declared as a global Pandemic by World Health Organization. Liver impairment has been frequently reported as common manifestation particularly in patient with underlying chronic liver disease and other comorbidities.

The name "Corona" was coined by June Almeida and David Tyrrell who first observed and studied human coronaviruses in the year of 1964[1].

In the early observational studies liver related complications of SARS-CoV-2, a varying degree of liver function tests showed abnormalities in the affected patients. Literature has shown that patients with severe COVID-19 disease have high risk of liver injury than that of non-severe disease [2,3]

Liver enzyme indices including: ALT (Alanine transaminase), AST (Aspartate aminotransaminase). Also, other liver function test parameters like TB (Total bilirubin) and Albumin have been elevated and reported according to several studies [3,17,28]. The mechanisms of liver injury that occur in COVID-19 infection remain unclear. Our current understanding suggests that infection of highly pathogenic human coronavirus may result in the liver injury by direct virus-induced cytopathic effects and/or immunopathology induced by overshooting inflammatory responses.

Causes of liver injury in COVID-19:

Du M et al found that SARS-CoV-2 directly binds to the hepatocytes. As ACE-2 (Angiotensin converting enzyme 2) does not express on hepatocytes, it leads to increase in the liver enzymes, but it is unlikely to cause the liver injury. Few studies reported that ACE2 is expressed on both the liver cells and bile duct cells [4,5]. Although a preliminary study revealed that the expression of ACE2 is more on the cholangiocytes (59.7%) than on the hepatocytes (2.6%), which promotes to increase the liver injury [6]. In COVID-19 cases, few studies showed increase in the serum pro-inflammatory cytokine and cytokinine levels [7–9].

Pathological findings of liver biopsies in patients with CoV-2 infection showed moderate micro vesicular steatosis and mild lobular and portal activity has caused the liver injury. Furthermore studies [10–13] suggested drug hepatotoxicity is one of the causes for liver injury. Multiple drugs like antibiotics, antivirals, antipyretics, analgesics and steroids are potential causes [14,15]

Only few studies described a slight elevation of TB levels and ALP in the C0V-2 infection [3,16,17].

The purpose of the study is to review the pattern of changes or variation in the liver enzymes during the course of the disease/ covid 19 infection.

METHOD:

A literature review used online data base in PubMed, Lancet, Journal of Hepatology searched title is "COVID-19" and 20577 relevant journals were found by searching database among them. We selected 15 international journals from the list which had original articles related to changes in liver enzymes in COVID-19. Median age 47 years (Inter QuarantileRange 33-61). In one study age is included in both case and controls. The median age for case is 72.5 years, for control 67 years (Inter QuarntileRange 24-94).[38] The percentage of men was more in all the studies when compared with women and children. [3,10,16,29,38] On the day of admission and during hospitalization, LFT was done in COVID-19 patients. LFT levels were increased during the hospitalization period. The age group and cut off for LFT is based on the Institutional board of the "National Health Commission of China".

RESULT:

The following descriptive studies showed alternations in the liver enzymes, such as Aspartate Transaminase (AST), Alanine animotransferase (ALT), Alkaline Phosphatase (ALP) and Total Bilirubin (TB).Cut off values for LFT: T-bill: 0-21 µmol/L AST: 15-40 U/L ALT: 9-50 U/L ALP: 0-135 U/LGGT: 0-49 U/L.[3,10,16,25,37]3Based on the above criteria, the day of admission and during the hospitalization,

patients were classified into severe and non-severe COVID disease.
Liver enzymes are increased in severe disease than in the non-severe patients. It is also increased in the ICU patients than the non-ICU patients with the COVID infection.

- Guan at al [3] and colleagues have studied 1099 patient from 552 hospitals, out of which 22.2% (168/757) showed abnormal AST levels, 21.3% (158/741) showed abnormal ALT levels. They have also observed that AST and ALT levels are elevated in both severe and non-severe disease patients.
- Among 168 patients, whose AST levels are increased, (18.2%) 112 patients are with non-severe disease and (39.4%) 56 are with severe disease. Among 158 patients with elevated ALT levels, (28.1%) are with severe disease and (19.8%) was higher than in mild disease.
- According to Wang et al [18] the AST and ALT levels showed mild elevation in 138 patients and as well as Cao et al [19] also stated that AST and ALT levels are elevated only in 128 patients with severe disease.
- Chen at al [16] studied 99 cases of COVID-19 infection and reported with elevated transaminases levels, total bilirubin and albumin levels. Out of 99 patients, 28 patients showed elevated ALT levels, 35 showed elevated AST levels, 18 and 97 patients showed elevated total bilirubin and albumin levels.
- And also, the Wu et al [20] studied 280 patients, among them the abnormal ALT 7(2.5%). There was no difference in liver function between mild/moderate patient and severe/critically ill patient (P>0.05)
- Zhou at al [21] studied 191 patients and found that the Abnormal ALT 59/189 (39.2%) Elevated ALT levels were associated with death.
- According to Wan et al [22] around 135 patients among them the Abnormal AST 30/135 (22.2%) There was no difference in the level of ALT and TB compared mild with severe patient.
- And Zhang et al 115 patients' [23] Abnormal ALT 11 (9.6%) Abnormal AST 17 (14.8 %) Abnormal GGT 15(13.0 %) Abnormal TB 3(2.6%) There was no difference in liver function index (AST, ALT, TB and GGT) after admission to ICU.

The Li et al [9] studies show Abnormal ALT 33(38.8%) Abnormal AST 33(38.8%) Moderate and
severe patients were more likely to have liver injury According to Guan et al, Li et al and Zhang et al studies (3,9,23) COVID patients with pre-existing liver disorder showed remarkably increased SGPT and SGOT levels.
We have analysed 2,279 patients with pre-existing liver disease, where AST elevation is seen in 371(25.53%) patients, and elevated ALT levels are seen in 401(23.87%) patients.

Liver enzymes elevated in non-existing

According to Zhou et al [21] and Zhang et al [26] studies, COVID-19 patients without having pre liver disease has showed less transaminase enzymes (SGOT, SGPT). We have analyzed 532 patients with non-pre-existing disease, where AST levels were elevated in 100 (26.6%) and ALT levels were elevated in 129 (21.7%) patients.

DISCUSSION:

Covid -19 and liver enzymes:

Several studies have shown different degree of elevated serum liver enzymes such as ALT, AST, GGT, ALP and total bilirubin in Covid-19 patients. Mainly indicated by abnormal ALT and AST levels accompanied by slightly elevated total bilirubin. Infact the incidence of the ALT and AST range from 2.5%- 50% (ALT), 2.5%- 61.1% (AST). With regard to total bilirubin reported increased level 0%-35.3% of cases [3,17]. Relevant elevation of ALP and GGT levels have not been reported in most of the studies. However, Ji et al (28) examined 202 patients with confirmed COVID-19. 37.6% of which with non-alcoholic fatty acid liver disease (NAFLD) and shows that elevated GGT levels protend a more severe causes of disease.
It remains unclear whether liver injury is caused by the virus itself or reflects a severe inflammatory response with liver damage [29].

Some of the studies says that ACE-2 (Angiotensin converting enzyme 2) variations in hepatocytes (2.6%) and in cholanginocytes (59.7%). It says said COVID 19 might bind to ACE-2 positive cholangiocytes to disregulate liver functions.

COVID-19- Related liver enzymes in children

Children have a special and high-level immune response system with distinct clinical feature in COVID-19 [30]. Qiu et al analyzed 36 pediatric patients age (0-16 years) with laboratory confirmed COVID-19. Among them only 2 children have recorded with elevated liver enzymes [31]. Wang et al studied 31 cases of SARS-CoV-2 infection in children from six provinces in northern China and reported 22.2% of patients with elevated transaminases levels, being the highest value registered of ALT and AST 69 U/L and 67 U/L respectively [6].

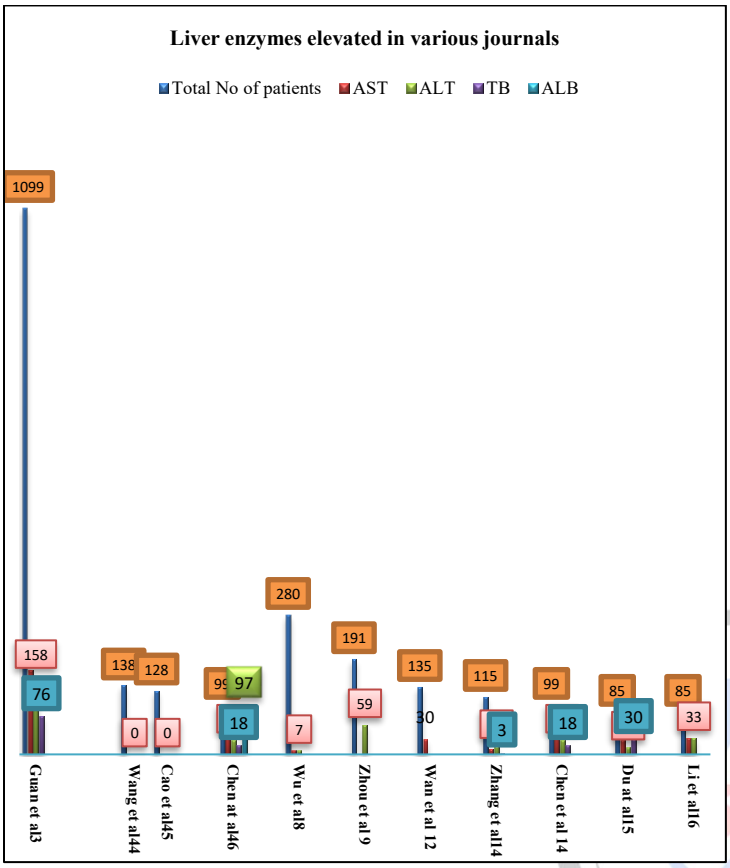
COVID-19 and pre-occurring liver disease:

The covid-19 is found that higher risk for chronic liver disease, it may be due to immunodeficiency.[2] Current published description studies shows that only small numbers of Covid-19 patients have been underlined chronic liver disease and no statistically significant association has been outcome [32–35]
A case of series from Lombardy region in Italy that described the characteristic of covid-19 patient admitted to intensive care units reported patient with chronic liver disease accounting for only 3% [36]. Another study from China described a population of COVID-19 patients with 2.1% of patient shaving underlying hepatitis B found that it is associated with more severe COVID-19 disease [3].
In reference to Table No1 and graph No 1, we have taken the average of the AST, ALT and TB. The results we found out such as, 38.9% of ALT elevated, 47.5 % of AST significantly higher than other liver enzyme, along with a moderate elevation of total bilirubin around 26.5%.

Table No.1: Liver enzymes elevated in various Journals

Sl. NO	Disease	Reference	No of patients analyzed	Manifestation	Note
1	Covid -19	Guan et al[3]	1099	Abnormal AST, 168/757(22.2%) Abnormal ALT,158/741(21.3) Abnormal TB 76/722(10.5)	The proportional of abnormal AST in severe cases (39.4) was markedly higher then mild cases(18.2)
2		Wang et al[18]	138	Mild elevation of AST and ALT	
3		Cao et al[19]	128	Abnormal ALT and AST only in severe patient	
4		Chen at al[16]	99	Abnormal ALT-28 (28%) Abnormal AST -35 (35%) Abnormal TB -18 (18%) Abnormal ALB -97 (98%)	Difference in liver function between mild/moderate patient and severe/critically ill patient
5		Wu et al[20]	280	Abnormal ALT 7 (2.5%)	There was no difference in liver function between mild/moderate patient and severe/critically ill patient
6		Zhou et al [21]	191	Abnormal ALT 59/189 (39.2%)	Elevated ALT levels were associated with death
7		Wan et al [22]	135	Abnormal AST 30/135(22.2%)	There was no difference in the level of ALT and TB compared mild with sever patient
8		Zhang et al[23]	115	Abnormal ALT 11(9.6%) Abnormal AST 17 (14.8 %) Abnormal GGT 15(13.0 %) Abnormal TB 3(2.6%)	There was no difference in liver function index after admission to ICU
9		Du at al[24]	85	Abnormal ALT 14 (16.5%) Abnormal AST 28 (32.9%) Abnormal TB 30 (35.3%)	All patients were deceased cases
10		Li et al[9]	85	Abnormal ALT 33(38.8%) Abnormal AST 33(38.8%)	Moderate and severe patients were more likely to have liver injury

Graph No.1: Liver enzymes elevated in various Journals



CONCLUSION:

Covid-19 is new corona virus infection leading to acute respiratory infection with liver manifestation along with increase in the cytokine activity associated with high rate of morbidity and mortality in the patients.In this review we summarize the report of liver enzymes elevationis caused by COVID-19 infection: by the action of Angiotensin converting enzyme-2(ACE-2), which expresses on the hepatocytes and choliangiocytes, which promotes to increase the liver injury.Liver enzymes are elevated in both Pre-existing liver disease andNon-existing liver infection. Less significant is seen non-existing liver infection.In this study we have analysed that ALT enzyme activity is higher than AST during the course of COVID -19 infection. And also, bilirubin levels have showed significant increase during the infection.

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